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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,757	11/27/2001	Jon Thorson	2653/52	7539

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EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	PAPER NUMBER
1637	10

DATE MAILED: 08/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,757	THORSON ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/8/2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-103* is/are pending in the application.

4a) Of the above claim(s) *92-103* is/are withdrawn from consideration.

5)☒ Claim(s) *29-91* is/are allowed.

6)☒ Claim(s) *1-3,5,7-10,12,13,15-17,19,21-24,26 and 27* is/are rejected.

7)☒ Claim(s) *4,6,11,14,18,20,25 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's preliminary amendment and drawings filed in Paper No. 6 on February 3, 2003 is acknowledged.

Election/Restrictions

2. Applicant's election without traverse of Group I, claims 1-93, in Paper No. 9 is acknowledged. Claims 92-103 have been withdrawn from consideration as being drawn to a non-elected invention.

Information Disclosure Statement

The information disclosure (IDS) statement filed in Paper No. 7 is acknowledged. However, two of the references (DE 198 58 588 A1 and WO 95/32181 (*Abstract considered only*) have not been considered because Applicant failed to provide a translation of the claimed references and thus no meaningful interpretation of the information referred to therein could be ascertained. It is suggested submitting a translation of those references for consideration of the information referred to therein.

Specification

3. The disclosure is objected to because of the following informalities:

(a) The priority document is not listed in the first sentence on the first page of the specification (see 37 CFR 1.78(a) and MPEP 201.11). It is suggested amending the disclosure to recite the priority information in the first sentence of the specification.

(b) The specification contains brackets at pages 25, 28, 29 and 31 not intended to encompass an amendment (see 37 CFR 1.121 (e)(2)(ii)). It is suggested removing the brackets from the specification.

(c) The specification contains a blank space at page 26 in the center of the page.

(d) The use of the trademark "Taqman" at page 4 of the specification has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention

(a) Claim 6 is indefinite at the recitation of "claim A5" because it cannot be clearly determined what prior claim(s) applicant is making reference to. It is suggested amending the claim to recite proper dependency.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 1-3, 5, 9, 12, 13, 15-17, 19, 23, 26 and 27 are rejected under 35 U.S.C. 102(a) as being anticipated by Li et al. (Nucleic acids Research, Vol. 28, No. 11,

pages e52 (i-v). Regarding claims 1 and 15, Li et al. teaches a process for measuring the activity of a nucleic acid cleavage agent and for detecting a nucleic acid cleavage agent present in a sample, the process comprising: incubating the sample with a probe, the probe comprising (i) an oligonucleotide that forms a stem loop structure, (ii) a fluorophore and (iii) a quencher, wherein the fluorophore and the quencher are positioned such that the fluorophore fluoresces less when the probe is intact than when the probe is cleaved; measuring the level of fluorescence of the probe and correlating the amount with the activity of the nucleic acid cleavage agent (page e52 (i) column 2, last paragraph to page e52 (ii) column 1, lines 1-22).

8. Regarding claims 2, 3, 5, 16, 17 and 19, Li et al. teach wherein the nucleic acid cleavage agent is an enzyme and wherein the enzyme is a nuclease or endonuclease (S1 nuclease, Mung Bean Nuclease and Dnase I) (page e52 (ii), beginning at the 5th and 6th lines from the bottom of column 1).

9. Regarding claims 9 and 23, Li et al. teach wherein the nucleic acid cleavage agent cleaves the probe in the single stranded portion of the stem loop structure (page e52 (ii), col. 1, lines 3-5 and Figure 1).

10. Regarding claims 12, 13, 26 and 27, Li et al. teach wherein the fluorophore and quencher are coupled to the 5' end and 3' end of the probe (page e52 (i), beginning at the 4th through 6th line from the bottom of column 2). Li et al further teach wherein the nucleic acid cleavage agent cleaves the probe at a site between the quencher and the fluorophore (see Figure 1, diagram and legend). Therefore Li et al meet the limitations of claims 1, 2, 3, 5, 9, 12, 13, 15-17, 19, 23, 26 and 27 of the instant invention.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 7, 8, 10, 21, 22, 24, are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. as previously applied above to claims 1, 2, 3, 5, 9, 12, 13, 15-17, 19, 23, 26 and 27 in view of Battigello et al. (Bioorganic and Medicinal Chemistry, Vol. 3, No. 6, pages 839-849, June 1995). Regarding claims 7, 8, 21, 22, Li et al. teach process comprising: incubating a sample containing a nucleic acid cleavage agent with a probe, the probe comprising (i) an oligonucleotide that forms a stem loop structure, a fluorophore and a quencher, wherein fluorophore and the quencher are positioned such that the fluorophore fluoresces less when the probe is intact than when the probe is cleaved; and measuring the level of fluorescence of the probe and correlating amount of fluorescence when the probe is cleaved; measuring the level of fluorescence of the probe;

and correlating amount of fluorescence with activity of the nucleic acid cleavage agent. Li et al also teaches wherein the cleavage agent is an enzyme which cleaves single stranded nucleic acid molecules.

14. Li et al differ from the instant invention in that Li et al do not expressly teach wherein the cleavage agent is a small molecule or wherein the cleavage agent is enediyne. However, Li et al. provides motivation for using other enzymes and/or molecules in the method in the teaching that the method developed here is convenient and accurate in detecting the influences of various catalytic conditions on DNA cleavage. In a general teaching, Battigello et al teach the use of the small molecule enediyne to cleave single-stranded nucleic acid molecules. Battigello et al teach wherein the enediyne compounds exhibit cleavage of an RNA substrate near the 5' end and cleavage in a single stranded loop region of the RNA substrate (abstract). Therefore in view of the foregoing, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention that the enediyne et al compounds as taught by Battigello et al could be used in the molecular beacon-based cleavage assay of Li et al. to cleave the hairpin-shaped oligonucleotides based on the teaching of Battigello et al that the enediyne compounds are capable of cleaving single stranded loop regions of a nucleic acid substrate.

Regarding claim 10, 24, Li et al teach wherein DNAse I is used to cleave the probe in the single-stranded portion of the stem loop structure. Li et al further teach that DNA can digest both single and double stranded DNA and thus the fluorophore and quencher in the molecular beacon should be separated from each other after DNAse I digestion (page e52 (ii), column 2, lines 5-8). Therefore, since Li et al. teach the use of DNAse I in the molecular beacon-based assay. Battigello et al discloses wherein the enediyne

compounds are capable of cleaving nucleic acids in the double stranded and single stranded conformation (abstract and page 843, column 2, lines 14-17). Therefore, it would have been obvious to one of ordinary skill in the art that the nucleic acid cleavage agent as taught by Li et al and Battigello et al cleaves the nucleic acid probe (substrate) in the single stranded and double stranded conformation.

Conclusion

15. Claims 1-3, 5, 7-10, 12, 13, 15-17, 19, 21-24, 26, 27 are rejected. Claims 4, 6, 11, 14, 18, 20, 25 and 28 are objected. Claims 29-91 are free of the prior art. The claims contain allowable subject matter because prior art does not teach or suggest wherein the process of evaluating activity of a nucleic acid cleavage agent or detecting the presence of a nucleic acid cleavage agent in a sample comprises incubating the sample with a probe, wherein the probe comprises an oligonucleotide that forms a stem loop structure and a recognition site for the nucleotide cleavage agent; a fluorophore and quencher. The prior art also does not teach wherein multiple probes comprising an oligonucleotide that forms a stem loop structure is utilized in method of evaluating activity of a nucleic acid cleavage agent or detecting the presence of a nucleic acid cleavage agent in a sample. Likewise the prior art does not further teach wherein a nucleotide protective agent is added to the mixture comprising a nucleotide cleavage agent and a probe comprising an oligonucleotide that forms a stem loop structure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (703) 305-1680. The examiner can normally be reached on Monday through Thursday from 9:30 am to 6:30 pm and on Friday from 9:30 am to 1:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308 0196.

Cynthia B. Wilder, Ph.D.
Examiner
Art Unit 1637

cbw
August 15, 2003